

PATENT COOPERATION TREATY

PCT

REC'D	20 OCT 1999
WIPO	PCT

18

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

85705


Applicant's or agent's file reference HKA-1025	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US98/02007	International filing date (day/month/year) 04/02/1998	Priority date (day/month/year) 04/02/1997
International Patent Classification (IPC) or national classification and IPC C07H21/00		
Applicant KOSTER, Hubert		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.
 - ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 03/09/1998	Date of completion of this report 03/09/1998
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Gohlke, P Telephone No. (+49-89) 2399 8549



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US98/02007

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-16 as originally filed

Claims, No.:

1-52 as originally filed

Drawings, sheets:

1/10-10/10 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
☒ claims Nos. 1, 3, 4, 12, 14-52.

because:

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- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 1, 3, 4, 12, 14-52.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:
 - ☐ restricted the claims.
 - ☐ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☒ neither restricted nor paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
 - ☐ complied with.
 - ☒ not complied with for the following reasons:
4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:
 - ☐ all parts.
 - ☒ the parts relating to claims Nos. 2, 5-11, 13.

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V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims
	No:	Claims 2, 5-11, 13
Inventive step (IS)	Yes:	Claims
	No:	Claims 2, 5-11, 13
Industrial applicability (IA)	Yes:	Claims 2, 5-11, 13
	No:	Claims

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Section VII:

The subject-matter claimed in main **claim 2** does not satisfy the requirements of article 6 PCT for the following reasons:

1) The definition of the wording "reversible linkage" is ambiguous. In the description, the applicant gives some examples of what may be reversible linkages (see page 9, first paragraph) however without providing any limiting definition. Whilst not strictly essential to give a wholly limiting definition, it would clearly have provided a much better basis for ascertaining the scope of protection sought.

Moreover, most linkages can be reversed, it just depends on how strong the conditions used are. Indeed a reversible linkage may just be a bond or even part of the biopolymer.

2) With regard to the scope of claim 2, it has been understood that it involves the following variants:

a) the two biopolymers may be linked to the insoluble support at different places, and only one needs to have a reversible linkage.

b) the two biopolymers can be linked **together** by any linkage thus forming longer biopolymers, and as long as they are linked to an insoluble support via a reversible linkage, they fall within the scope of claim 2.

c) the two biopolymers may or may not be identical biopolymers.

3) There are a number of discrepancies between the description and the claims. Whilst the claims relate to at least two biopolymers comprised of nucleic acids conjugated onto a solid support via a reversible linkage, the description seems to indicate that the scope of protection sought, and the problem to be solved by the present application are considerably different from the broadest scope of the claims. To this respect, the description pertains to (see pages 2 and 3):

- link proteins to nucleic acids, in which there is supposedly no specific reproducible linkage known in the art, under controlled attachment site and controlled stoichiometry based on the specific and strong interaction between chelators in the presence of metal ions,

- conjugate at least two biopolymers to an insoluble support by **two different** reversible linkages, which are cleavable under **selective** conditions,

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EXAMINATION REPORT - SEPARATE SHEET**

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- provide methods for reversible immobilization of nucleic acid molecules, in which case, the nucleic acid can carry a series of imidazolyl functionalities in a format which makes them available for chelation and which does not interfere with Watson-Crick base pairing and the other conjugating partner molecule can carry the chelator functionality.

Section V:

Reference is made to the following documents:

D1 = WO 85/04674

D2 = US-A-5 547 835

D3 = WO 90/01564

D4 = Citations "Biotechniques, vol. 6, no. 8, 1 Jan. 1988, pages 768-770 and 773-775".

D5 = US-A-5 410 068

D6 = DE 3644346.

The subject-matter of claims 2, 5-11 and 13 is not novel for the following reasons:

1) Claim 2:

As a result of the above lack of clarity objections (see section VII above and in particular point 2)b) thereof):

- any nucleic acid-matrix system for the immobilization of nucleic acids anticipates the subject-matter of claim 2 (see for example **D1**; claim 1), and any method for the purification of nucleic acid fragments comprising the reversible immobilization of the nucleic acid fragments on a solid support involves a composition as claimed in present claim 2 and thus anticipates the subject-matter of claim 2 (see for example **D2**; claims 1, 3 and 34).

- any nucleic acid hybridization assay anticipates the subject-matter of claim 2 in that it comprises at least two identical nucleic acid probes covalently bound to the solid surface, preferably through spacer arms, or it comprises at least two distinct nucleic acid probes such that their base sequences are complementary to at least two different regions of a target polynucleotide (see for example **D3**; claims 1, 8 and 23).

- any solid-phase oligonucleotide synthesis that utilizes phosphoramidite synthesis

chemistry to assemble sequences on derivatized solid support involves a composition as claimed in present claim 2 and thus anticipates the subject-matter of claim 2 (see for example **D4**).

- any polymerase chain reaction (PCR) used to amplify a nucleic acid sequence involves the immobilization of PCR amplified products to a solid support being performed by using labeled primers involves a composition as claimed in present claim 2 and thus anticipates the subject-matter of claim 2 (see for example **D5**; see in particular example 9 in combination with example 7).

- any method for the purification of nucleic acids using affinity chromatography on a derivatized solid support involves a composition as claimed in present claim 2 and thus anticipates the subject-matter of claim 2 (see for example **D6**).

- finally, any combinatorial library falls within the scope of claim 2.

The above cited documents do not represent an exhaustive supply of ones detailing compositions which fall within the scope of claim 2 - merely a sample designed to show some of the known diversity of compositions within this scope.

2) Claim 5:

Claimed subject-matter refers to a composition according to the one claimed in claim 2 wherein the reversible linkage is specified. This preferred embodiment is anticipated at least by **D2**: see claim 34 and col. 11, lines 52-56, wherein the reversible linkage is a photocleavable bond; or by **D3**, claims 74, 75.

3) Claims 6-10:

Claimed subject-matter refers to a composition according to the one claimed in claim 2 wherein the insoluble support is specified. These preferred embodiments are anticipated at least by **D2**: see col. 14, second paragraph, wherein the insoluble supports are e.g. beads (silica gel, controlled pore glass, magnetic beads, Sephadex/Sepharose beads, cellulose beads, etc.), capillaries, glass fiber filters, glass surfaces, metal surfaces or plastic material; or by **D3**, claims 3-6; or by **D4**, see Title.

4) Claim 11:

Claimed subject-matter refers to a composition according to the one claimed in claim 2 wherein the nucleic acids are specified. These preferred embodiments are anticipated at least by **D2**; see col. 12, lines 57-62, wherein the nucleic acids can be natural

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oligoribo- or oligodeoxyribonucleotide as well as analogs (thio-modified phosphodiester or phosphotriester backbone) or oligonucleotide mimetics such as PNA.

5) Claim 13:

Claimed subject-matter refers to a composition according to the one claimed in claim 2 wherein it is specified that there is a spacer between the nucleic acid and the insoluble support. This preferred embodiment is anticipated at least by **D2**; see col. 11, lines 52-55; or by **D3**, claim 8; or by **D4** wherein the spacer is a long chain alkylamine LCCA.

6) With respect to the preceding paragraphs 2)-5), the prior art documents cited therein do not represent an exhaustive supply of ones detailing compositions which fall within the scope of claims 5-11 and 13 - merely a sample designed to show some of the known diversity of compositions within this scope.

Therefore, the subject-matter of claims 2, 5-11 and 13 do not meet the requirements of article 33(2) PCT.

In case this application is proceeded in the European phase and the applicant is able to restore novelty, then he would be invited to substantiate grounds of inventive step concerning the remaining novel subject-matter.

Section VI:

Certain published documents (Rule 70.10)

Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO 98/20020	14.05.98	06.11.97	06.11.96
			23.01.97
			08.10.97

WO 98/20020 does not constitute prior art within the meaning of Rule 64.1.

It is mentioned herein within the meaning of rules 64.3 and 70.10 PCT.; no check was made whether its priorities have been validly claimed.

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Section VIII:

On page 5, in the first line of the last paragraph, it appears that the wording "soluble support" is not correct and leads to a lack of clarity; it is assumed that it is meant to represent a "solid support". Correction is requested (Article 6 PCT).

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :

C07H 21/00

A2

(11) International Publication Number:

WO 98/33808

(43) International Publication Date:

6 August 1998 (06.08.98)

(21) International Application Number: PCT/US98/02007

(22) International Filing Date: 4 February 1998 (04.02.98)

(30) Priority Data:

60/037,165

4 February 1997 (04.02.97)

US

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1640 Monument Street, Concord, MA 01742 (US).(74) Agents: ARNOLD, Beth, E. et al.; Foley, Hoag & Eliot LLP,
One Post Office Square, Boston, MA 02109 (US).(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR,
BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE,
GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO,
NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR,
TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, GM,
KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ,
BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE,
CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN,
ML, MR, NE, SN, TD, TG).**Published***Without international search report and to be republished
upon receipt of that report.*

(54) Title: A REVERSIBLE STOICHIOMETRIC PROCESS FOR CONJUGATING BIOMOLECULES

(57) Abstract

Compositions comprised of at least two biopolymers (e.g., nucleic acids or polypeptides), which are conjugated to an insoluble support by two different reversible linkages, which are cleavable under selective conditions, as well as methods and components for producing the same are described.

FOR THE PURPOSES OF INFORMATION ONLY

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PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark
Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 22 September 1998 (22.09.98)	
International application No. PCT/US98/02007	Applicant's or agent's file reference HKA-1025
International filing date (day/month/year) 04 February 1998 (04.02.98)	Priority date (day/month/year) 04 February 1997 (04.02.97)
Applicant KOSTER, Hubert	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

03 September 1998 (03.09.98)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Christelle Croci Telephone No.: (41-22) 338.83.38
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PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference HKA-1025	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 98/ 02007	International filing date (day/month/year) 04/02/1998	(Earliest) Priority Date (day/month/year) 04/02/1997
Applicant KOSTER, Hubert		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.
☐ It is also accompanied by a copy of each prior art document cited in this report.

1. ☐ Certain claims were found unsearchable (see Box I).
2. ☒ Unity of invention is lacking (see Box II).
3. ☐ The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
 - ☐ filed with the international application.
 - ☐ furnished by the applicant separately from the international application,
 - ☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
 - ☐ Transcribed by this Authority
4. With regard to the title,
 - ☒ the text is approved as submitted by the applicant.
 - ☐ the text has been established by this Authority to read as follows:
5. With regard to the abstract,
 - ☒ the text is approved as submitted by the applicant.
 - ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.
6. The figure of the **drawings** to be published with the abstract is:
 - Figure No. _____ ☐ as suggested by the applicant.
 - ☐ because the applicant failed to suggest a figure.
 - ☐ because this figure better characterizes the invention.
 - ☒ None of the figures.

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
2,11(completely); 1,5-10, 13(partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 2,11 completely; 1,5-10,13 partially

Composition comprising at least two biopolymers conjugated to an insoluble support by at least one reversible linkage. Wherein the at least two biopolymers are comprised of nucleic acids.

2. Claims: 3,12 completely; 1,5-10,13 partially

Composition comprising at least two biopolymers conjugated to an insoluble support by at least one reversible linkage. Wherein the at least two biopolymers are comprised of polypeptides.

3. Claims: 4,14-28 completely; 1,5-10,13 partially

Composition comprising at least two biopolymers conjugated to an insoluble support by at least one reversible linkage. Wherein the at least two biopolymers are comprised of nucleic acid and a protein.

4. Claims: 1,5-10,13 partially

Composition comprising at least two biopolymers conjugated to an insoluble support by at least one reversible linkage. Wherein the at least two biopolymers are not comprised of two nucleic acids, two polypeptides, or a nucleic acid and a protein.

5. Claims: 29,30,33,36

Oligonucleotides comprised of a B-cyanoethylphosphoramidite.

6. Claims: 31,32,34,35

Oligonucleotides comprised of a heterobifunctional trityl group.

7. Claims: 37,38

Nucleoside triphosphates with a chelate functionality on the base moiety

8. Claims: 39-41

Recombinant proteins with enzymatic activity.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

9. Claims: 42,43

A peptide with a chelator at the N or C terminus.

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International Application No

PCT/US 98/02007

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07H21/00 C12Q1/68 A61K47/00 G01N33/543 C12N11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07H C12Q A61K G01N C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 89 05616 A (BIO METRIC SYSTEMS INC) 29 ✓ June 1989 see the whole document ---	1,2, 5-10,13
X	US 5 410 068 A (COULL JAMES M ET AL) 25 April 1995 see the whole document ---	1,2, 5-10,13
X	US 5 582 981 A (TOOLE JOHN J ET AL) 10 December 1996 see abstract; claim 1 ---	1,2,5-9
X	WO 85 04674 A (LIFE TECHNOLOGIES INC) 24 ✓ October 1985 see claims 1-33 ---	1,2,13

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search

22 October 1998

Date of mailing of the international search report

07. 01. 99

Name and mailing address of the ISA

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Authorized officer

SCOTT, J

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/02007

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 90 01564 A (MICROPROBE CORP) 22 February 1990 see page 1-84	1,2,5-9, 13
A	ARSHADY E: "BEADED POLYMER SUPPORTS AND GELS II. PHYSICO-CHEMICAL CRITERIA AND FUNCTIONALIZATION" JOURNAL OF CHROMATOGRAPHY, vol. 586, no. 2, 22 November 1991, pages 199-219, XP000247969 see the whole document	6-9
A	PON R T ET AL: "DERIVATIZATION OF CONTROLLED PORE GLASS BEADS FOR SOLID PHASE OLIGONUCLEOTIDE SYNTHESIS" BIOTECHNIQUES, vol. 6, no. 8, 1 January 1988, pages 768-770, 773 - 775, XP000562920 see the whole document	1,2, 5-10,13
A	US 5 547 835 A (KOESTER HUBERT) 20 August 1996	1,2,13
A	DE 36 44 346 A (SAEULENTECHNIK DR ING HERBERT) 21 May 1987 see the whole document	1,2, 5-10,13
A	SCOUTEN W H ET AL: "REVERSIBLE IMMOBILIZATION OF ANTIBODIES ON MAGNETIC BEADS" ANALYTICAL BIOCHEMISTRY, vol. 205, no. 2, 1 September 1992, pages 313-318, XP000296795 see the whole document	1,5-10, 13
A	P.D.GERSHON ET AL.: "Stable Chelating Linkage for Reversible Immobilization of Oligohistidine Tagged Proteins in the BIAcore Surface Plasmon Resonance Detector." JOURNAL OF IMMUNOLOGICAL METHODS, vol. 183, 1995, pages 65-76, XP002081778	1
E	WO 98 20020 A (KOSTER HUBERT ;LITTLE DANIEL P (US); SEQUENOM INC (US); CANTOR CHA) 14 May 1998 see claims 1-121	1,2, 5-10,13

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/02007

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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